# APPENDIX A

## MINIMAL RISK LEVEL (MRL) WORKSHEET

| | |
|---|---|
| Chemical name(s): | Ethylene glycol |
| CAS number(s): | 107-21-1 |
| Date: | December 1995 |
| Profile status: | Third Draft Post Public Comment |
| Route: | [X] Inhalation [ ] Oral |
| Duration: | [X] Acute [ ]Intermediate [ ] Chronic |
| Key to figure: | 4 |
| Species: | Mouse |

MRL: 0.5 [ ] mg/kg/day [X] ppm [ ] $mg/m^3$

Reference: Tyl 1988a

Experimental design: Timed-pregnant CD-1 mice were exposed to ethylene glycol aerosol on gestational days (Gd) 6–15, 6 hours per day by nose-only procedures at doses of 0, 500, 1,000, or 2,500 $mg/m^3$ (0, 197, 394, or 985 ppm) target concentration. Control animals were exposed to water aerosol (4,200 $mg/m^3$ or 5,705 ppm). Females were weighed, observed daily for clinical signs, and evaluated for water consumption. At sacrifice on Gd 18, females were evaluated for body weight, gravid uterine weight, and liver and kidney weight. Ovarian corpora lutea were counted and all uterine implantation sites evaluated. Maternal body weight was unaffected. No dose-related clinical signs were noted. Water consumption was not significantly affected. At sacrifice, liver weight was not affected. Absolute maternal kidney weight was increased at 394 and 985 ppm and relative maternal kidney weight was increased at 985 ppm, but no treatment related lesions were observed.

Effects noted in study and corresponding doses: A clear dose response relationship was observed for absolute and relative kidney weight:

197 ppm EG = low dose (NOAEL)
394 ppm EG = mid dose (increased absolute kidney weight; less serious LOAEL)
985 ppm EG = high dose (increased absolute and relative kidney weight)

Dose endpoint used for MRL derivation:

[X] NOAEL [ ] LOAEL

Uncertainty factors used in MRL derivation:

[ ] 1 [ ] 3 [ ] 10 (for use of a LOAEL)
[ ] 1 [ ] 3 [X] 10 (for extrapolation from animals to humans)
[ ] 1 [ ] 3 [X] 10 (for human variability)

Was a conversion factor used from ppm in food or water to a mg/body weight dose?
If so, explain: No conversion was used.

APPENDIX A

If an inhalation study in animals, list conversion factors used in determining human equivalent dose:
1) Doses in animals were converted from $mg/m^3$ to ppm:

500 $mg/m^3$ x 24.45/62.07 (mol. wt. EG) = 197 ppm; 1,000 $mg/m^3$ = 394 ppm;
2,500 $mg/m^3$ = 985 ppm

Was a conversion used from intermittent to continuous exposure?
If so, explain: Doses were converted from a 6 hours per day exposure to a continuous exposure by multiplying by 6/24:

197 ppm x 6/24 = 49.4 ppm;
394 ppm x 6/24 = 98.5 ppm;
985 ppm x 6/24 = 246.2 ppm

Other additional studies or pertinent information that lend support to this MRL: Tyl (1988) was a study designed to determine a NOAEL for inhalation by nose-only exposure. A previously conducted study (Tyl 1985), used whole body exposure, but was considered flawed due to the possibility of ingestion of ethylene glycol from the fur of exposed animals through grooming. Thus, Tyl (1988) used the most conservative exposure paradigm for inhalation studies, which lends greater credence to the assumption that the observed effects were due to inhalation of the compound, only. In this regard, metabolic acidosis and renal toxicity are the hallmarks of ethylene glycol toxicity. Both these effects arise from the metabolism of ethylene glycol to glycolic acid (acidosis) and oxalate (oxalate nephrosis). Frank renal toxicity from ethylene glycol is usually accompanied by the observation of oxalate crystals in the renal tissue and in the urine. In Tyl (1988), oxalate nephrosis was not observed. However, increased kidney weight has been observed in conjunction with oxalate nephrosis in other studies after oral exposure (DePass et al. 1986a; Woodside 1982). It may be assumed that since the increase in kidney weight showed a dose response relationship, and was detected in the absolute kidney weight at the mid-dose, but as both absolute and relative kidney weight at the high-dose, that the increase in kidney weight observed is related to renal toxicity. In addition, the developmental evaluation of the offspring from this study indicate a NOAEL at the mid-dose and reduced fetal body weight and increased incidence of skeletal variations at the high-dose. Developmental effects from ethylene glycol appear to be the result of maternal metabolic acidosis (Khera et al. 1991). It appears that in the mouse, the maternal kidney was the most sensitive indicator of those parameters evaluated. Of the available acute inhalation studies, Tyl (1988) had the highest NOAEL that was associated with a dose-related effect. It is notable that the LOAEL for maternal toxicity in this study is equal to the NOAEL for developmental toxicity in this study. Effects observed in humans suggest a similar MRL. For instance, in Wills et al. (1974), male volunteers experienced upper respiratory tract irritation after a 15-minute exposure to ethylene glycol in ambient air at 55 ppm; doses above 79 ppm were not tolerated.

Agency Contact (Chemical Manager): Ed Murray

APPENDIX A

# MINIMAL RISK LEVEL WORKSHEET

Chemical name(s): Ethylene glycol
CAS number(s): 107-21-1
Date: December 1995
Profile status: Third Draft Post Public Comment
Route: [ ] Inhalation [X] Oral
Duration: [X] Acute [ ]Intermediate [ ] Chronic
Key to figure: 48
Species: mouse

MRL: 2.0 [X] mg/kg/day [ ] ppm [ ] $mg/m^3$

Reference: Tyl 1989

Experimental design: Timed-pregnant CD-1 mice were given ethylene glycol by gavage on Gd 6–15. Females were weighed, observed daily for clinical signs, and evaluated for water intake. At sacrifice on Gd 18, females were evaluated for body weight, gravid uterine weight, and liver and kidney weight. Kidneys from control and high-dose dams were examined microscopically. Uterine contents were evaluated. There were no significant effects on the number of corpora lutea per dam; the number of total, nonviable, or viable implants per litter;, or on sex ratio. Fetal body weights per litter were reduced only at 1,500 mg/kg/day. There was no increase in the incidence of individual or total external or visceral malformations in any group relative to the vehicle control. There was a significant increase in the incidence of two skeletal malformations (fused ribs or thoracic arches) in the 1,500 mg/kg/day group, and the incidences of pooled skeletal malformations and all malformations were significantly increased in this group as well. The incidence of total malformations per litter was also significantly increased at 500 mg/kg/day. There were no significant increases in individual external or visceral variations, or in pooled external, visceral or skeletal variations or in total variations. The incidences of 23 skeletal variations were increased in the 1,500 mg/kg/day group. One skeletal variation (bilateral extra rib 14) was also increased at 500 mg/kg/day.

Effects noted in study and corresponding doses: A dose-related increase in developmental toxicity was observed:

150 mg/kg/day EG = low dose (NOAEL)

500 mg/kg/day EG = mid dose (increased incidence of total malformations and one skeletal variation - bilateral extra rib 14; Serious LOAEL)

1,500 mg/kg/day EG = high dose (reduced fetal body weight, increased incidence of 2 skeletal malformations (fused ribs or thoracic arches), increased incidences of pooled skeletal malformations and all malformations, increased incidence of 23 skeletal variations)

Dose endpoint used for MRL derivation:

[X] NOAEL [ ] LOAEL

Uncertainty factors used in MRL derivation:

[ ] 1 [ ] 3 [ ] 10 (for use of a LOAEL)
[ ] 1 [ ] 3 [X] 10 (for extrapolation from animals to humans)
[ ] 1 [ ] 3 [X] 10 (for human variability)

Was a conversion factor used from ppm in food or water to a mg/body weight dose?
If so, explain: No conversion was used.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose:
No conversion was used.

Was a conversion used from intermittent to continuous exposure?
If so, explain: No conversion was used.

Other additional studies or pertinent information that lend support to this MRL: Other developmental studies have identified ethylene glycol as a developmental toxicant after oral administration in animals, which adversely affects the conceptus at levels that do not cause significant adverse effects in the maternal animal. In the cited study (Tyl 1989), the maternal NOAEL is 1,500 mg/kg/day, compared to a developmental NOAEL of 150 mg/kg/day. In mice, 750 mg/kg/day caused reduced litter size and increased incidence of skeletal malformations, but was a maternal NOAEL (Price et al. 1985). Neeper-Bradley (1990) detected an increase in skeletal malformations in rats treated orally with 1,000 mg/kg/day ethylene glycol on Gd 6–15, with a NOAEL for developmental effects of 500 mg/kg/day. The maternal NOAEL in that study was 2,500 mg/kg/day. Similarly, Price et al. (1985) determined a developmental LOAEL of 1,250 mg/kg/day (skeletal malformations) in rats treated orally during gestation, a dose that caused only a 17% decrease in body weight in the maternal dams. Thus, using oral exposure during the period of major organogenesis in the rodent (Gd 6–15), the developmental effects are the most sensitive end point.

Agency Contact (Chemical Manager): Ed Murray

APPENDIX A

# MINIMAL RISK LEVEL WORKSHEET

| | |
|---|---|
| Chemical Name: | Ethylene glycol |
| CAS Number: | 107-21-1 |
| Date: | December 1995 |
| Profile Status: | Third Draft Post Public |
| Route: | [ ] Inhalation [X] Oral |
| Duration: | [ ] Acute [ ] Intermediate [X] Chronic |
| Graph Key: | 65 |
| Species: | Rat |

MRL: 2.0 [X] mg/kg/day [ ] ppm

Reference: DePass et al. 1986a; Woodside 1982

Experimental design: Groups of 130 male and female rats were fed diets to achieve dosage goals of 0, 40, 200, or 1,000 mg/kg/day ethylene glycol for 24 months. Mortality, body weight, diet consumption, histopathological findings, and gross findings were monitored. No evidence of oncogenicity was found. High-dose males (1,000 mg/kg/day) died prior to the 18-month termination, with death attributable to oxalate nephrosis caused by ethylene glycol exposure. Calcium oxalate crystals were found in the urine of high-dose males and females at 12 months. Increased absolute and relative kidney weights were observed only in high-dose males at 12 months. At 12 months, high-dose males had chronic nephritis (including tubular dilation, and proteinosis, glomerular shrinkage, tubular cell hyperplasia, and chronic interstitial nephritis). These results were supported by hematological effects also reported in the same study. Males in the high-dose group had decreases in red blood cell (RBC) count, hematocrit, hemoglobin, and increases in neutrophils at 12 months. No effects were seen at the lower doses. Females had normal hematology. Males in the high-dose group had a 4-fold increase in (BUN) and creatinine at 12 months, but no changes were noted at lower dose levels. At 12 months, high-dose males showed increases in urine volume, and a reduction in urine specific gravity. The only change seen in the urinalysis of females at 12 months was a reduction in mean pH at the high-dose level. High-dose males exhibited a significant reduction in absolute and relative liver weight at 12 months. High-dose females, but not males, had mild fatty metamorphosis of the liver; organ weight was normal. Females had normal body weight gain; high-dose males had decreased weight gain at 12 months of treatment. Mineralization, but no other lesions and no other organ weight changes, was seen in heart, lungs, and stomach in males, but not in females.

Effects noted in study and corresponding doses: renal toxicity

200 mg/kg/day EG = mid dose (NOAEL)

1,000 mg/kg/day EG = high dose (100% mortality from oxalate nephrosis in males by 18 months; increased absolute and relative kidney weights in high-dose males at 12 months; males had chronic nephritis, including tubular dilation, and proteinosis, glomerular shrinkage, tubular cell hyperplasia, and chronic interstitial nephritis; calcium oxalate crystals in the urine of females)

Dose and endpoint used for MRL derivation:

[X] NOAEL [ ] LOAEL

Uncertainty Factors used in MRL derivation:

[ ] 10 for use of a LOAEL
[X] 10 for extrapolation from animals to humans
[X] 10 for human variability

Was a conversion used from ppm in food or water to a mg/body weight dose?
If so, explain: No conversion was used.

If an inhalation study in animals, list the conversion factors used in determining human equivalent dose:

Other additional studies or pertinent information that lend support to this MRL:
Other chronic feed studies report higher NOAEL and LOAEL values than those reported for rats in DePass et al. (1986a) and Woodside (1982). In mice treated for 24 months (DePass et al. 1986a) no adverse effects were seen at the high dose (1,000 mg/kg/day) in either males or females. In NTP (1982), male B6C3F1 mice exhibited oxalate nephrosis at 3,315 mg/kg/day, degeneration of the centrilobular hepatocytes at 1,625 mg/kg/day, and a NOAEL for hepatic effects of 812.5 mg/kg/day ethylene glycol for 2 years. In the same study, females showed hepatic and pulmonary effects at 6,500 mg/kg/day, with a NOAEL of 3,250 mg/kg/day.

The EPA (IRIS 1995) assigned ethylene glycol a reference dose (RfD) of 2.0 mg/kg/day with an uncertainty factor of 100 based on a NOAEL of 200 mg/kg/day kidney toxicity in rats (DePass et al. 1986a). The chronic-duration MRL developed by the Agency for Toxic Substances and Disease Registry for ethylene glycol is not in conflict with the current RfD for ethylene glycol.

Agency Contact (Chemical Manager): Ed Murray

APPENDIX A

# MINIMAL RISK LEVEL WORKSHEET

Chemical name(s): Propylene glycol
CAS number(s): 57-55-6
Date: December 1995
Profile status: Third Draft Post Public Comment
Route: [X] Inhalation [ ] Oral
Duration: [ ] Acute [ X]Intermediate [ ] Chronic
Key to figure: 1
Species: Rat

MRL: 0.009 [ ] mg/kg/day [X] ppm [ ] $mg/m^3$

Reference: Suber et al. 1989

Experimental design: Young, healthy adult Sprague-Dawley rats were divided into 4 groups of 19 males and 19 females each. Three groups were exposed for 5 days per week, 6 hours per day for 13 weeks by nose-only inhalation to mean target aerosol concentrations of 51, 321, or 707 ppm propylene glycol. The fourth, the control group, was exposed to humidified, filtered room air. Nasal hemorrhaging occurred in all exposed groups of male and female rats indicating that propylene glycol can act as a dehydrogenating agent. From week 2–14, the average of nasal hemorrhaging in male rats was <1%, 64%, 74%, and 75% in controls, low-exposure, medium-exposure, and high-exposure groups, respectively. In females, the average indices were < 1% in controls, 14% in the low-exposure group, and 71% in the medium and high-exposure groups. Animals recovered during non-exposure weekend periods. Similar trends were observed for ocular discharge, with females having generally less ocular discharge than males. A significant reduction in body weight of 5–7% starting on day 50 and continuing until the end of the study was observed in female rats receiving the highest dose of 707 ppm propylene glycol. Similar observation was made in the group receiving 321 ppm of propylene glycol but later in the study starting on day 64. This body weight reduction was correlated with a significant reduction in food consumption beginning on study day 43 and 50 for the high- and medium-exposure females, respectively. Female rats exposed to 321 ppm propylene glycol had a significant decrease in white blood cell count and lymphocyte numbers. Female rats exposed to 707 ppm propylene glycol had a significant decrease in hemoglobin concentration, white blood cell count and lymphocyte numbers. Male rats in the medium (321 ppm) and high (707 ppm) groups had a significant decrease in serum sorbitol dehydrogenase and gamma-glutamyl transferase. A significant decrease in total serum protein was observed in male rats treated with high (707 ppm) dose of propylene glycol while females treated with a medium (321 ppm) dose of propylene glycol had an increase in total serum protein. These changes were considered as being sporadic. Kidney weight was decreased at 321 ppm in both sexes. Although there were no treatment-related gross pathology changes, light microscopy revealed thickening of respiratory epithelium with increase in the number of goblet cells and their mucin content in both female and male animals receiving medium and high propylene glycol dose. Minute volume, tidal volume, and respiratory rates were not significantly altered in rats exposed to 51, 321, or 707 ppm propylene glycol for 13 weeks, suggesting that animals adapted to the exposure concentrations.

Effects noted in study and corresponding doses: Nasal hemorrhaging was observed in all PG-treated groups:

51 ppm PG = low dose (64% in males, 14% in females; less serious LOAEL)

321 ppm PG = mid dose (74% in males, 71% in females)

707 ppm PG = high dose (75% in males, 71% in females)

Dose endpoint used for MRL derivation:

[ ] NOAEL [X] LOAEL

Uncertainty factors used in MRL derivation:

[ ] 1 [ ] 3 [X] 10 (for use of a LOAEL)
[ ] 1 [ ] 3 [X] 10 (for extrapolation from animals to humans)
[ ] 1 [ ] 3 [X] 10 (for human variability)

Was a conversion factor used from ppm in food or water to a mg/body weight dose?
If so, explain: No conversion was used.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose:
Doses were converted from mg/L to ppm:

0.16 mg/L x 1,000 = 160 mg/$m^3$. 160 mg/$m^3$ x 24.45/ 76.09 (MW PG) = 51.4 ppm

1.0 mg/L = 321.3 ppm

2.2 mg/L = 706.9 ppm

Was a conversion used from intermittent to continuous exposure?
If so, explain: Animals were exposed for 6 hours per day, 5 days per week. Since the effect (nasal hemorrhaging) subsided when exposure was discontinued during the weekend periods, it seemed relevant to adjust the exposure period not only to a continuous 24 hour, but also to a 7-day exposure. Therefore conversion factors of 6/24 and 5/7 were used:

51 ppm x 6/24 x 5/7 = 9 ppm

Other additional studies or pertinent information that lend support to this MRL: This was the only suitable intermediate-duration inhalation exposure study available.

Agency Contact (Chemical Manager): Ed Murray

# APPENDIX B

# USER'S GUIDE

## Chapter 1

## Public Health Statement

This chapter of the profile is a health effects summary written in non-technical language. Its intended audience is the general public especially people living in the vicinity of a hazardous waste site or chemical release. If the Public Health Statement were removed from the rest of the document, it would still communicate to the lay public essential information about the chemical.

The major headings in the Public Health Statement are useful to find specific topics of concern. The topics are written in a question and answer format. The answer to each question includes a sentence that will direct the reader to chapters in the profile that will provide more information on the given topic.

## Chapter 2

## Tables and Figures for Levels of Significant Exposure (LSE)

Tables (2-l) 2-2, and 2-3) and figures (2-1 and 2-2) are used to summarize health effects and illustrate graphically levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, differences in response by species, minimal risk levels (MRLs) to humans for noncancer endpoints, and EPA's estimated range associated with an upper-bound individual lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. Use the LSE tables and figures for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of No-Observed-Adverse-Effect Levels (NOAELs), Lowest-Observed-Adverse-Effect Levels (LOAELs), or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE Table 2-l and Figure 2-l are shown. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

## LEGEND

### See LSE Table 2-1

(1) Route of Exposure One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. When sufficient data exists, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure, i.e., inhalation, oral, and dermal (LSE Table 2-1, 2-2, and 2-3, respectively). LSE figures are'limited to the inhalation (LSE Figure 2-l) and oral (LSE Figure 2-2) routes. Not all substances will have data on each route of exposure and will not therefore have all five of the tables and figures.

(2) Exposure Period Three exposure periods - acute (less than 15 days), intermediate (15 to 364 days), and chronic (365 days or more) are presented within each relevant route of exposure. In this example, an inhalation study of intermediate exposure duration is reported. For quick reference to health effects occurring from a lmown length of exposure, locate the applicable exposure period within the LSE table and figure.

(3) Health Effect The major categories of health effects included in LSE tables and figures are death, systemic, immunological, neurological, developmental, reproductive, and cancer. NOAELs and LOAELs can be reported in the tables and figures for all effects but cancer. Systemic effects are further defined in the "System" column of the LSE table (see key number 18).

(4) Key to Figure Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 18 has been used to derive a NOAEL and a Less Serious LOAEL (also see the 2 "18r" data points in Figure 2-l).

(5) Species The test species, whether animal or human, are identified in this column. Section 2.4 , "Relevance to Public Health," covers the relevance of animal data to human toxicity. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.

(6) Exposure Frequency/Duration The duration of the study and the weekly and daily exposure regimen are provided in this column. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 18), rats were exposed to ethylene glycol and propylene glycol via inhalation for 6 hours per day, 5 days per week, for 3 weeks. For a more complete review of the dosing regimen refer to the appropriate sections of the text or the original reference paper, i.e., Nitschke et al. 1981.

(7) System This column further defines the systemic effects. These systems include: respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, and dermal/ocular. "Other" refers to any systemic effect (e.g., a decrease in body weight) not covered in these systems. In the example of key number 18, 1 systemic effect (respiratory) was investigated.

(8) NOAEL A No-Observed-Adverse-Effect Level (NOAEL) is the highest exposure level at which no harmful effects were seen in the organ system studied. Key number 18 reports a NOAEL of 3 ppm for the respiratory system which was used to derive an intermediate exposure, inhalation MRL of 0.005 ppm (see footnote "b").

(9) LOAEL A Lowest-Observed-Adverse-Effect Level (LOAEL) is the lowest dose used in the study that caused a harmful health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific endpoint used to quantify the adverse effect accompanies the LOAEL. The respiratory effect reported in key number 18 (hyperplasia) is a Less serious LOAEL of 10 ppm. MRLs are not derived from Serious LOAELs.

(10) Reference The complete reference citation is given in chapter 8 of the profile.

(11) CEL A Cancer Effect Level (CEL) is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiologic studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses not causing measurable cancer increases.

(12) Footnotes Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. Footnote "b" indicates the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.005 ppm.

## LEGEND

See Figure 2-1

LSE figures graphically illustrate the data presented in the corresponding LSE tables. Figures help the reader quickly compare health effects according to exposure concentrations for particular exposure periods.

(13) Exposure Period The same exposure periods appear as in the LSE table. In this example, health effects observed within the intermediate and chronic exposure periods are illustrated.

(14) Health Effect These are the categories of health effects for which reliable quantitative data exists. The same health effects appear in the LSE table.

(15) Levels of Exposure concentrations or doses for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure concentration or dose is measured on the log scale "y" axis. Inhalation exposure is reported in mg/m3 or ppm and oral exposure is reported in mg/kg/day.

(16) NOAEL In this example, 18r NOAEL is the critical endpoint for which an intermediate inhalation exposure MRL is based. As you can see from the LSE figure key, the open-circle symbol indicates to a NOAEL for the test species-rat. The key number 18 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 3 ppm (see entry 18 in the Table) to the MRL of 0.005 ppm (see footnote "b" in the LSE table).

(17) CEL Key number 38r is 1 of 3 studies for which Cancer Effect Levels were derived. The diamond symbol refers to a Cancer Effect Level for the test species-mouse. The number 38 corresponds to the entry in the LSE table.

(18) Estimated Upper-Bound Human Cancer Risk Levels This is the range associated with the upper-bound for lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. These risk levels are derived from the EPA's Human Health Assessment ‚Group's upper-bound estimates'of the slope of the cancer dose response curve at low dose levels ($q_l$*).

(19) Key to LSE Figure The Key explains the abbreviations and symbols used in the figure.

SAMPLE

1 →

## TABLE 2-1. Levels of Significant Exposure to [Chemical x] – Inhalation

| Key to figure[a] | Species | Exposure frequency/ duration | System | NOAEL (ppm) | LOAEL (effect) Less serious (ppm) | LOAEL (effect) Serious (ppm) | Reference |
|---|---|---|---|---|---|---|---|
| 2 → INTERMEDIATE EXPOSURE | | | | | | | |
| | 5 | 6 | 7 | 8 | 9 | | 10 |
| 3 → Systemic | ↓ | ↓ | ↓ | ↓ | ↓ | | ↓ |
| 4 → 18 | Rat | 13 wk 5d/wk 6hr/d | Resp | 3[b] | 10 (hyperplasia) | | Nitschke et al. 1981 |
| CHRONIC EXPOSURE | | | | | | | |
| | | | | | 11 | | |
| | | | | | ↓ | | |
| Cancer | | | | | | | |
| 38 | Rat | 18 mo 5d/wk 7hr/d | | | 20 | (CEL, multiple organs) | Wong et al. 1982 |
| 39 | Rat | 89–104 wk 5d/wk 6hr/d | | | 10 | (CEL, lung tumors, nasal tumors) | NTP 1982 |
| 40 | Mouse | 79–103 wk 5d/wk 6hr/d | | | 10 | (CEL, lung tumors, hemangiosarcomas) | NTP 1982 |

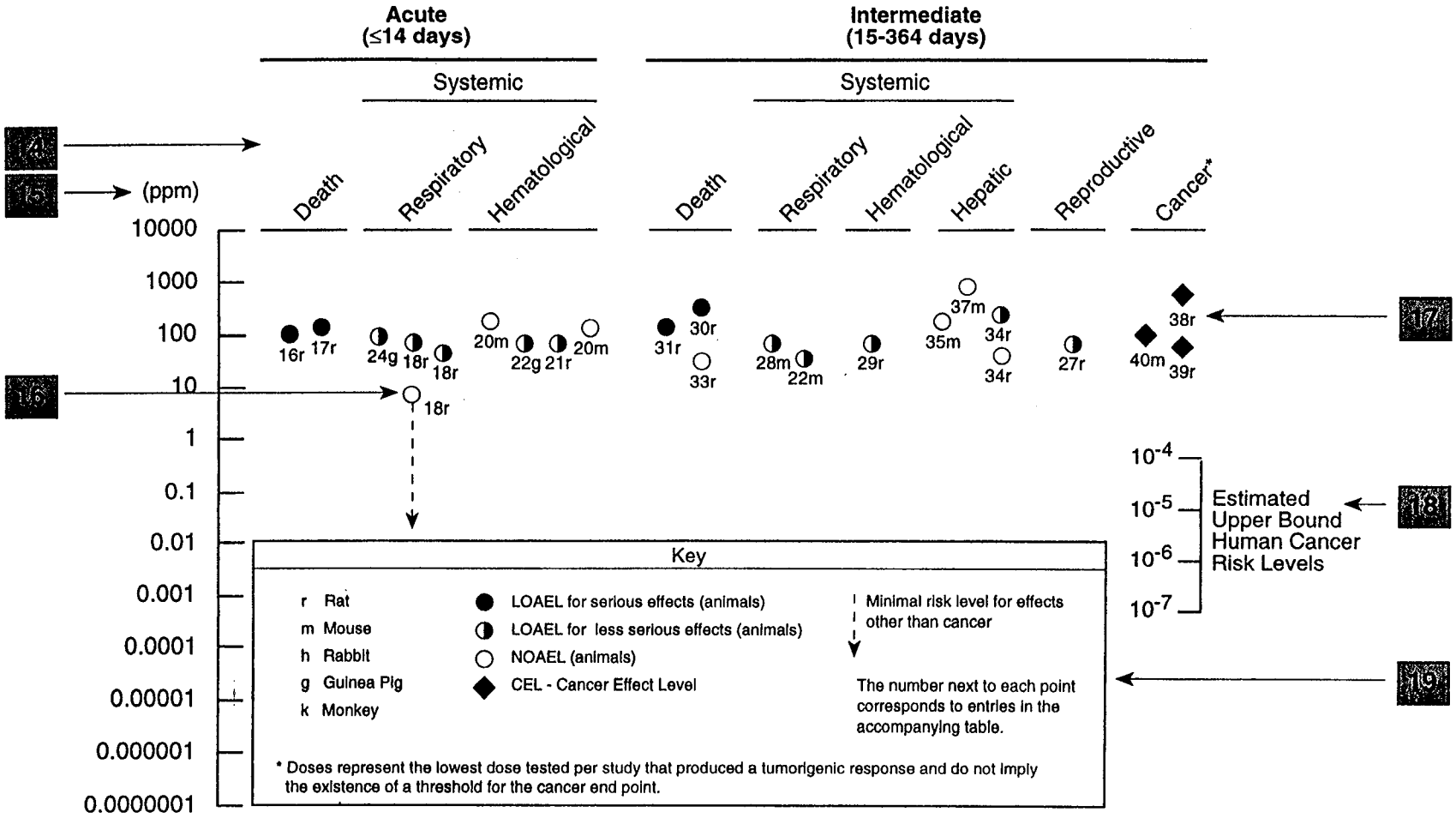
[a] The number corresponds to entries in Figure 2-1.

12 → [b] Used to derive an intermediate inhalation Minimal Risk Level (MRL) of 5 x $10^{-3}$ ppm; dose adjusted for intermittent exposure and divided by an uncertainty factor of 100 (10 for extrapolation from animal to humans, 10 for human variability).

CEL = cancer effect level; d = days(s); hr = hour(s); LOAEL = lowest-observed-adverse-effect level; mo = month(s); NOAEL = no-observed-adverse-effect level; Resp = respiratory; wk = week(s)

SAMPLE

## Figure 2-1. Levels of Significant Exposure to [Chemical X] – Inhalation



APPENDIX B

## Chapter 2 (Section 2.4)

### Relevance to Public Health

The Relevance to public Health section provides a health effects summary based on evaluations of existing toxicologic, epidemiologic, and toxicokinetic information. This summary is designed to present interpretive, weight-of-evidence discussions for human health endpoints by addressing the following questions.

1. What effects are known to occur in humans?

2 . What effects observed in animals are likely to be of concern to humans?

3. What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

The section covers endpoints in the same order they appear within the Discussion of Health Effects by Route of Exposure section, by route (inhalation, oral, dermal) and within route by effect. Human data are presented first, then animal data. Both are organized by duration (acute, intermediate, chronic). *In vitro* data and data from parenteral routes (intramuscular, intravenous, subcutaneous, etc.) are also considered in this section. If data are located in the scientific literature, a table of genotoxicity information is included.

The carcinogenic potential of the profiled substance is qualitatively evaluated, when appropriate, using existing toxicokinetic, genotoxic, and carcinogenic data. ATSDR does not currently assess cancer potency or perform cancer risk assessments. Minimal risk levels (MRLs) for noncancer endpoints (if derived) and the endpoints from which they were derived are indicated and discussed.
Limitations to existing scientific literature that prevent a satisfactory evaluation of the relevance to public health are identified in the Data Needs section.

### Interpretation of Minimal Risk Levels

Where sufficient toxicologic information is available, we have derived minimal risk levels (MRLs) for inhalation and oral routes of entry at each duration of exposure (acute, intermediate, and chronic). These MRLs are not meant to support regulatory action; but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans. They should help physicians and public health officials determine the safety of a community living near a chemical emission, given the concentration of a contaminant in air or the estimated daily dose in water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicologic information on which the number is based. Chapter 2.4, “Relevance to Public Health,” contains basic information lmown about the substance. Other sections such as 2.6, “Interactions with Other Chemicals”, and 2.7, “Populations that are Unusually Susceptible” provide important supplemental information.

APPENDIX B

To derive an MRL, ATSDR generally selects the most sensitive endpoint which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential systemic, neurological, and developmental effects. If this information and reliable quantitative data on the chosen endpoint are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest NOAEL that does not exceed any adverse effect levels. When a NOAEL is not available, a lowest-observed-adverse-effect level (LOAEL) can be used to derive an MRL, and an uncertainty factor (IF) of 10 must be employed. Additional uncertainty factors of 10 must be used both for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a substance-specific MRL are provided in the footnotes of the LSE Tables.

# APPENDIX C

# ACRONYMS, ABBREVIATIONS, AND SYMBOLS

| | |
|---|---|
| ACGIH | American Conference of Governmental Industrial Hygienists |
| ADME | Absorption, Distribution, Metabolism, and Excretion |
| atm | atmosphere |
| ATSDR | Agency for Toxic Substances and Disease Registry |
| BCF | bioconcentration factor |
| BSC | Board of Scientific Counselors |
| C | Centigrade |
| CDC | Centers for Disease Control |
| CEL | Cancer Effect Level |
| CERCLA | Comprehensive Environmental Response, Compensation, and Liability Act |
| CFR | Code of Federal Regulations |
| CLP | Contract Laboratory Program |
| cm | centimeter |
| CNS | central nervous system |
| d | day |
| DHEW | Department of Health, Education, and Welfare |
| DHHS | Department of Health and Human Services |
| Dl | deciliter |
| DOL | Department of Labor |
| ECG | electrocardiogram |
| EEG | electroencephalogram |
| EPA | Environmental Protection Agency |
| EKG | see ECG |
| F | Fahrenheit |
| $F_1$ | first filial generation |
| FAO | Food and Agricultural Organization of the United Nations |
| FEMA | Federal Emergency Management Agency |
| FIFRA | Federal Insecticide, Fungicide, and Rodenticide Act |
| fpm | feet per minute |
| ft | foot |
| FR | Federal Register |
| g | gram |
| GC | gas chromatography |
| gen | generation |
| HPLC | high-performance liquid chromatography |
| hr | hour |
| IDLH | Immediately Dangerous to Life and Health |
| IARC | International Agency for Research on Cancer |
| ILO | International Labor Organization |
| in | inch |
| Kd | adsorption ratio |
| kg | kilogram |
| kkg | metric ton |
| $K_{oc}$ | organic carbon partition coefficient |

| | |
|---|---|
| $K_{ow}$ | octanol-water partition coefficient |
| L | liter |
| LC | liquid chromatography |
| $LC_{Lo}$ | lethal concentration, low |
| $LC_{50}$ | lethal concentration, 50% kill |
| $LD_{Lo}$ | lethal dose, low |
| $LD_{50}$ | lethal dose, 50% kill |
| LOAEL | lowest-observed-adverse-effect level |
| LSE | Levels of Significant Exposure |
| m | meter |
| mg | milligram |
| min | minute |
| mL | milliliter |
| mm | millimeter |
| mm Hg | millimeters of mercury |
| mmol | millimole |
| mo | month |
| Mosm | milliosmolal |
| mppcf | millions of particles per cubic foot |
| MRL | Minimal Risk Level |
| MS | mass spectrometry |
| NIEHS | National Institute of Environmental Health Sciences |
| NIOSH | National Institute for Occupational Safety and Health |
| NIOSHTIC | NIOSH's Computerized Information Retrieval System |
| ng | nanogram |
| nm | nanometer |
| NHANES | National Health and Nutrition Examination Survey |
| nmol | nanomole |
| NOAEL | no-observed-adverse-effect level |
| NOES | National Occupational Exposure Survey |
| NOHS | National Occupational Hazard Survey |
| NPL | National Priorities List |
| NRC | National Research Council |
| NTIS | National Technical Information Service |
| NTP | National Toxicology Program |
| OSHA | Occupational Safety and Health Administration |
| PEL | permissible exposure limit |
| pg | picogram |
| pmol | picomole |
| PHS | Public Health Service |
| PMR | proportionate mortality ratio |
| ppb | parts per billion |
| ppm | parts per million |
| ppt | parts per trillion |
| REL | recommended exposure limit |
| RfD | Reference Dose |
| RTECS | Registry of Toxic Effects of Chemical Substances |
| sec | second |
| SCE | sister chromatid exchange |

| | |
|---|---|
| SIC | Standard Industrial Classification |
| SMR | standard mortality ratio |
| STEL | short term exposure limit |
| STORET | STORAGE and RETRIEVAL |
| TLV | threshold limit value |
| TSCA | Toxic Substances Control Act |
| TRI | Toxics Release Inventory |
| TWA | time-weighted average |
| U.S. | United States |
| UF | uncertainty factor |
| yr | year |
| WHO | World Health Organization |
| wk | week |

| | |
|---|---|
| > | greater than |
| ≥ | greater than or equal to |
| = | equal to |
| < | less than |
| ≤ | less than or equal to |
| % | percent |
| α | alpha |
| β | beta |
| δ | delta |
| γ | gamma |
| μm | micron |
| μg | microgram |